Remarks

Claims 1, 6-7, 10 and 12-13 are amended. The amendments to the claims are intended to clarify Applicant's invention and are not intended to limit the equivalents to which any claim element may be entitled. No new matter is added by way of these amendments. Claims 1-8 and 10-13 are currently pending in this application.

With regards to item 3 on page 2 of the instant Office Action, color drawings and a Petition under 37 C.F.R. § 1.84(a)(2), for acceptance of color drawings, are supplied herewith. Additionally, the specification is amended hereinabove to insert the paragraph requested by the Examiner.

In item 4 on page 3 of the instant Office Action, the Examiner objected to Figures 2 and 11. The color drawings provided herewith render the objection moot. Therefore, Applicant respectfully requests withdrawal of the objection to the drawings.

In item 5 on page 3 of the instant Office Action, the Examiner objected to the specification. In particular, the Examiner objected to the Brief Description of the Drawings. Applicant respectfully submits that the amendments to the specification render the objection moot. Therefore, Applicant respectfully requests withdrawal of the objection to the specification.

In item 6 on page 4 of the instant Office Action, the Examiner objected to the specification under 35 U.S.C. 132(a) as containing new matter. Applicant respectfully submits that the amendments to the specification render the objection moot. Therefore, Applicant respectfully requests withdrawal of the objection to the specification.

The Claim Objections

Claims 6 and 7 were objected to for the reasons listed in item 7 on page 4 of the instant Office Action. Applicant respectfully submits that the amendments to claims 6 and 7 render the objection moot. Therefore, Applicant respectfully requests withdrawal of the objection to claims 6 and 7.

The 37 C.F.R. § 112, second paragraph, Rejections

The Examiner rejected claim 10 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant thanks the Examiner for suggesting an amendment to claim 10. Applicant has amended claim 10 as suggested by the Examiner. Applicant respectfully submits that the amendment to claim 10 renders the rejection moot. Therefore, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112(2) rejection of claim 10.

The Examiner rejected claims 10-13 under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps. Applicant respectfully submits that the amendments to claims 12-13 render the rejection moot. Therefore, Applicant respectfully requests withdrawal of the 35 U.S.C. § 112(2) rejection of claims 10-13.

The 37 C.F.R. § 112, first paragraph, Rejection

The Examiner rejected claims 1-8 and 10-13 under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

The Examiner alleges that the specification is not enabling for any non-polarized cell line transfected with any other DNA encoding an uptake transporter or DNA encoding an export pump. As amended, claim 1 recites "[a] polarized cell line double-transfected with (a) a DNA sequence encoding an uptake transporter for organic anions from the solute carrier (SLC) superfamily operatively linked with a promoter and (b) a DNA sequence encoding an export pump from the ATP-binding cassette (ABC) superfamily for organic anions or anionic conjugates operatively linked with a promoter." Applicant respectfully submits that with respect to non-polarized cell lines, the amendment to claim 1 renders this portion of the rejection moot.

With regards to uptake transporters and export pumps, it is demonstrated in the specification that double-transfected polarized cells expressing a recombinant uptake transporter for organic anions and an ATP-dependent export pump for anionic ions or anionic conjugates are able to transfer a substrate transcellular from the basolateral to the apical compartment at a

transfer rate several times faster than by single-transfected cells (see *e.g.*, the paragraph overlapping pages 3 and 4).

Applicant respectfully disagrees with the Examiner's statement that there can be no assurance that any pumps would be functional in the invention, because the different pumps have different acitivities. The fact that different pumps have different capacities does not mean that the pumps are functionally different. The capacity of a pump mainly depends on its affinity for the respective substrate. Fig. 8, to which the Examiner refers, clearly illustrates that the same combination of pumps, *i.e.*, MRP2 and OATP8, achieves transfer rates ranging from approximately 20 pmol/min/mg (Fig. 8B) to more than 400 pmol/min/mg (Fig. 8C) depending on the kind of substrate employed.

Further, the different transfer rates of BSP of approximately 290 pmol/min/mg with the MRP2/OATP8 system (Fig. 8A) compared with approximately 6 pmol/min/mg with the MRP2/OATP2 system (Fig. 13) are not surprising considering that the different affinities of OATP8 and OATP2 for BSP were known (see page 2, lines 27-34). On the other hand, both Fig. 8A as well as Fig. 13 show that in both double-transfected cells (MRP2/OATP8 and MRP2/OATP2) an approximately 3-fold increase of the BSP transfer rate was obtained compared with either OATP8 or OATP2 single-transfected cells. Hence, both double-transfected cells (MRP2/OATP8 and MRP2/OATP2) achieved a similar relative increase regarding the protein transfer rate (as OATP2 transports lower amounts of BSP into the cell, naturally only lower amounts of BSP can be exported from the cell with the MRP2/OATP2 system).

Moreover, the OAT1/MRP2 pump illustrated in Fig. 12 relates to a different substrate (PAH) and to a different model system (renal secretion and not hepatic secretion as OATP/MRP). Also, Fig. 12 shows that the transport rate of the double-transfected OAT1/MRP2 cell is approximately 2-fold higher than the transport rate of the OAT1 single-transfected cell. Thus, Fig. 12 demonstrates that the invention also works in a renal secretion model.

Consequently, it has been shown for all working examples that the protein transfer rate is significantly increased by the double-transfected cells according to the invention compared with respective single-transfected cells and that all working examples of double-transfected cells work according to the invention. Thus, it is respectively submitted that the assumption of the

Examiner, that the three models (OATP2/MRP2, OATP8/MRP2 and OAT1/MRP) are functionally different, is not justified, because in all cases the transcellular transport of organic anions was significantly increased in the double-transfected cells compared with the respective single-transfected cells.

As amended, the uptake transporters of claim 1 are limited to members of the solute carrier superfamily and the export pumps are limited to members of the ATP-binding cassette superfamily. Members of the solute carrier superfamily and the ATP-binding cassette superfamily, respectively, exhibit common structural and functional features and were characterized prior to the effective filing date of the instant application (e.g., see König et al, *Biochimica Biophysica Acta* 1999; König et al., *Journal of Biological Chemistry* 2000; both cited in the IDS). In particular, it was known that uptake transporters from the solute carrier superfamily mediate the uptake of organic anions into the cell and that export pumps belonging to ATP-binding cassette superfamily mediate the ATP-dependent excretion from cells. Thus, the function of the members of the solute carrier superfamily and the ATP-binding cassette superfamily, respectively, as transport proteins was established in the art. The specification sufficiently guides a skilled person that a polarized cell double-transfected with an uptake transporter from the solute carrier family and an export pump from the ATP-binding cassette superfamily enables a transcellular transport of organic anions at significant higher rates than single-transfected cells. The specification illustrates that this vectorial transport can be achieved with renal transport systems (*e.g.*, OAT1/MRP2) as well as with hepatic transport systems (*e.g.*, OATP/MRP2). A person of skill in the art can therefore expect from the teaching of the specification that the combination of a basolateral uptake transporter of the solute carrier superfamily with an export pump from the ATP-binding cassette superfamily in a polarized cell can mediate transcellular transport of organic anions at a higher rate than a single-transfected cell. Thus, no undue experimentation is necessary to make the invention with the defined classes of transport proteins from the solute carrier superfamily and the ATP-binding cassette superfamily.

It is respectfully submitted that § 112(1) requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims and this requirement has clearly been met. Thus, it is respectfully submitted that the pending

claims are in conformance with 35 U.S.C. § 112, first paragraph. Thus, withdrawal of the rejection of claims 1-8 and 10-13 under 35 USC § 112, first paragraph, is respectfully requested.

The Examiner rejected 1-8 and 10-13 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicant respectfully traverses this rejection.

The Examiner further contends that the claims do not comply with the written description requirement, because there is no description regarding common structural features of either uptake transporters or export pumps. Transport proteins for organic anions of the solute carrier superfamily and the ATP-binding cassette superfamily, respectively, were well characterized in the art (see *e.g.*, see König et al, *Biochimica Biophysica Acta* 1999; König et al., *Journal of Biological Chemistry* 2000; both cited in the IDS). Thus, the correlation between members of the solute carrier superfamily and the ATP-binding cassette superfamily, respectively, and their function as transport proteins for organic anions was established. The transport proteins specified in the application, i.e., OAT1, OATP2, OATP8, OATP-B, BSEP and MRP2 are from the different subgroups of the solute carrier superfamily and the ATP-binding cassette superfamily. Therefore, the specified transport proteins are representative of the generic invention. Again, the fact that transport proteins within a family differ in their affinities for a particular substrate resulting in different transport kinetics for that substrate, does not mean that the transport proteins are functionally different, because the inventors have demonstrated that polarized cells double-transfected with various combinations of an uptake transporter of the solute carrier superfamily and an export pump of the ATP-binding cassette superfamily mediate vectorial transport of organic anions at a significantly higher transfer rate than single-transfected cells.

Thus, it is respectfully submitted that the pending claims are in conformance with 35 U.S.C. § 112, first paragraph. Thus, withdrawal of the rejection of claims 1-8 and 10-13 under 35 USC § 112, first paragraph, is respectfully requested.

The 35 U.S. C. § 102(b) Rejection

The Examiner rejected claims 1-8 under 35 U.S.C. § 102(b) as being anticipated by Chazot (J. Biol Chem 269: 14403-24409 (1994)). Applicant respectfully traverses this rejection.

The standard for anticipation is one of strict identity, and to anticipate a claim for a patent a single prior art source must contain all its elements. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q.2d 90 (Fed. Cir. 1986); *In re Dillon*, 16 U.S.P.Q.2d 1987 (Fed. Cir. 1990). Furthermore, there must be no difference between the claimed invention and the disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991).

As amended, claim 1 recites "[a] polarized cell line double-transfected with (a) a DNA sequence encoding an uptake transporter for organic anions from the solute carrier (SLC) superfamily operatively linked with a promoter and (b) a DNA sequence encoding an export pump from the ATP-binding cassette (ABC) superfamily for organic anions or anionic conjugates operatively linked with a promoter."

Chazot et al. disclose double-transfected cells. However, the cells are not transfected with transport proteins (*e.g.*, a DNA sequence encoding an uptake transporter for organic anions from the solute carrier (SLC) superfamily and a DNA sequence encoding an export pump from the ATP-binding cassette (ABC) superfamily (claim 1)). Therefore, Chazot et al. do not anticipate the pending claims. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the 35 U.S.C. § 102(b) rejection of claims 1-8.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6905 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

YUNHAI CUI ET AL.

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies ~~that this~~ correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, ~~Alexandria~~, VA 22313-1450, on this 3rd day of April, 2006.

Patricia A. Heaton — Teresa A. Hoffman

Name Signature